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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/768,579	01/30/2004	Dale S. Dhanoa	24591-506	7318

30623 7590 02/06/2006

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EXAMINER	
BERNHARDT, EMILY B	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/768,579	DHANOA ET AL.	
	Examiner	Art Unit	
	Emily Bernhardt	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-97* is/are pending in the application.

4a) Of the above claim(s) *21-29,38,40,44,50,52,84,85 and 89-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,30-37,39,41-43,45-49,51,53-83 and 86-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants' election without traverse of species in claim 75 is acknowledged. However upon review of the compounds of formula (I) which contain a variety of species variously classified as well as individual species claims outside the scope of main claim 1 as well as multiple uses, the following restriction is being made.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20,30-37,39,41-43,45-49,51,53-83, and 86-88, drawn to compounds and compositions of formula (I) where both "Z" variables are carbons, classified in class 544, subclasses 360,392-394; class 514 subclasses 253.01, 255.03.

II. Claims 1-2,7-20,38,44,50,52,56 and 86-88, drawn to compounds, compositions of formula (I) where one or both "Z" variables are nitrogen(s), classified in class 544, subclasses 357,360,364; class 514 subclasses 252.11, 253.01.

III. Claim 40, drawn to pyrimidine species, classified in class 544, subclass 295.

IV. Claims 84-85, drawn to 3-substituted piperazine species, classified in class 544, subclass 382.

V. Claims 21-29 and 89-97, drawn to multiple uses employing compounds of Group I , classified in class 514, subclasses 253.01,etc.

VI. Claims 21-29 and 89-97, drawn to multiple uses employing compounds of Group II, classified in class 514, subclasses 252.11, etc.

The inventions are distinct, each from the other because of the following reasons: Compounds of I-IV are structurally dissimilar in view of the varying nature of rings permitted at the 1-position which are variously classified and would be expected to raise differing issues of patentability. Subject matter of Groups III and IV which are outside the scope of main claims 1 and 56 are directed to very narrow subject matter which have separate classification from that required for I-II and for IV the sulfonamide backbone is absent.

Inventions I-II and V-VI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case more than one use exists as can be seen at the very least from the method claims which from a reading of the specification includes Alzheimer's,

anxiety, ADD, Parkinson's Disease, disorders of the gastrointestinal tract, diseases of the bladder,etc. as well as uses taught by the prior art applied below. The claimed uses may raise additional issues of patentability- at the very least determining if the assays relied on herein are reasonably predictive for **in vivo treatment** for uses as varied and all encompassing as listed above.

Applicants' elected species falls within Group I. Applicants are advised that the claims will be examined **only** with respect to the subject matter of group I.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may**

result in a loss of the right to rejoinder. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The abstract of the disclosure is objected to because it does not depict the structural makeup of applicants' invention. Correction is required. See MPEP § 608.01(b).

Claims 1-20,30-37,39,41-43,45-49,51,53-83 and 86-88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. R4/R5 as "O" is not clear. It can be interpreted as meaning N-oxides or simply an incomplete dangling valence yet it appears nitro is intended and so should be inserted wherever this appears.

2. The definition of R6 needs to be made clearer. Is it just lower alkyl or after the semicolon are the additional recited moieties also part of R6 or really part of R4/R5?

3. The nature of atoms present in the joining of C- - - N is not fully set forth as only these 2 atoms are identified. Specification only exemplifies piperidino as being formed. Otherwise there is no guidance as to the nature of such rings. Note In re Wiggins 179 USPQ 421 regarding such terminology. Also what distinction is

being made by "cyclic" vs. "heterocyclic" ? Only heterocyclic rings can form since "N" is mandatory in the ring. See main claims 1 and 56.

4. "Esters" appearing throughout the main claims and independent species claims is unclear for more than one reason. Definition in specification (on p.15) includes "hetero atoms" can be present yet such are never identified. Also how are such esters attached to the remainder of the compounds? By way of COOH groups or pendant alkyl carbons or aromatic carbons? For species claims 30-37,39, 41-43,45-49,51,53-55,73-83 it not at all apparent how such esters can be attached as there are no COOH groups even present. Also the last part of the definition in the specification refers to alkyl,alkenyl,alkynyl groups as defined above but its not clear if or how these groups fit into the scope of esters.

5. The proviso appearing at the end of claim 1 is garbled. Note the last line is incoherent. Also, it appears the exclusions for R2/R3 depend on p being 0 as well as the conditions recited for R1 since dependent claims recite that R1 can be substituted phenyl. If this is correct, a "then" should replace "and" in front of "R2 and R3".

6. In claim 2 is said resulting "aryl" referring to the "Z" containing ring or something else?

7. In claim 7 "said...alkoxy" is not seen in main claim 1. Also see claim 61 which depends on 56.

8. For claims 8 and 62, a cycloalkyl ring can never have only 1 or 2 carbons. The ranges should be corrected to read as C_3-C_6.

9. For claim 10 the 3 cycloalkylalkyl groups recited are outside the scope of claim 9 from which 10 depends.

10. Scope of claims 13-17 as well as 68-72 is completely unknown since type of testing can be varied as well as conducted in different environments- *in vitro* vs *in vivo* using different animal cells and thus determining what is and what is not within the intended scope is not easily discernible.

11. Claims 18-20 (as well as 86-88) appear to be substantial duplicates of each other since the only difference in the wording of the claims is the intended uses. Note that different intended uses is given no material weight in such claims . In re Tuominen 213 USPQ 89. Also note MPEP 2111.02.

12. For claims 30-37,39, 41-43,45-49,51,53-55, and 73-83, "a composition" is recited in the preamble which suggests that the claims are covering a mixture of the recited species and salt and/or esters. Is this really intended? Or is a pharmaceutical composition intended or are alternative compounds really intended? If the latter the preamble should be replaced with "a compound" and

"comprising" which is open-ended language be replaced by "which is" . Also "and" (1st occurrence) should be replaced with "or" .

13. In the species of claims 47 and 51 what is the significance of "C-" ? It appears the cyclohexyl group is attached to the methyl group. Should not the naming be "...cyclohexylmethane sulfonamide" ?

Claims 1-20, 56-72 and 86-88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Scope of piperazines covered by the generic claims is not adequately enabled. From a reading of the specification (pages 1-15) terms such as alkyl, aryl, cycloalkyl, alkenyl, acyl, etc. are not given their normal meanings but also include a plethora of substituents thereon. "Aryl" includes in addition to aromatic carbocyclics, 5- and 6-membered heteroaromatics that can be further fused. Additionally, there can be "conjugated" cyclic rings in R2 and R3 which appear to include fused "Z" rings. Also rings can form on nitrogen attached to sulfonyl. Compounds made and tested do not represent such a scope as they are phenyl piperazines having substituents such as those recited in claim 2 corresponding to **unsubstituted** alkyls and cycloalkyls

with R1 being predominately tolyl or to a lesser extent cyclohexylmethyl and unsubstituted lower alkyl. The only example of a ring formed at C---N is piperidino. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves binding to one or more serotonin receptors. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved" and physiological activity is generally considered to be unpredictable. See In re Fisher 166 USPQ 18;

3) Direction or guidance- the compounds made and tested for 5-HT_{1A} agonist activity are not representative of the instant scope but are closer to each other than to remaining scope as discussed above;

4) State of the prior art- The compounds are piperazine derivatives substituted with a phenyl ring at one end that can have a variety of functional

groups permitted thereon as well as any type of substituted carbon in a ring or chain at the other end terminus which is linked to the central ring by way of sulfonylaminoalkylene or a ring interspersed at the sulfonamide nitrogen. While such compounds are known as evident from the art applied below, they are directed to only a small part of applicants' scope and for a variety of different uses (eg. as starting material, treating aggressive behavior, hypertension, cerebovascular disease) and thus do not evidence the many structural permutations permitted in the instant scope are known in the prior art for the same activity relied on herein;

5) Working examples- The limited test data presented for about 30 compounds of a homogeneous scope showed as much as a 100-fold spread for IC50 data and thus provides no clear indication of how the many untested functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1,2,7,8,12-20,56,61,62,66,68-72 and 86-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Uchida (Chemical abstract provided). Uchida describes compounds within the scope that serve as precursor as well as final products for the treatment of angina pectoris,etc. See compounds appended to the abstract which was obtained from a computer-assisted search. Note the "hydroxymethyl" species is the precursor while the final products corresponds to the nitrooxymethyl phenyl species. Applicants' definition of "alkyl" or "lower alkyl" includes substituted derivatives as can be seen on pages 10 and 13 of the specification. While nitrooxy is not particularly mentioned the scope for "substituted" is open-ended. Note the wording in the definition on p.10 "can include". "for example" .

Claims 13-17 as well as 68-72 are also rejected herein since reciting properties of anticipated compounds where the reference does not, does not preclude a rejection under 35 USC 102 or 103. Note the MPEP 2112 which states: "SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 195 USPQ 430 433 (CCPA 1977)."

Claims 1,2,7,8,11,13-20,56,61,62,65,68-72 and 86-88 are rejected under 35 U.S.C. 102(b) as being anticipated by Van Dalen (EP'089). The EP publication describes a compound within the instant scope for use in treating aggressive behavior. See eg.III on p.5. Note that the substituent "trifluoromethyl" on the phenyl ring is within the ambit of substituted alkyl and substituted lower alkyl as defined by applicants' specification . Claims 13-17 as well as 68-72 are also rejected herein for the same reason as discussed in the above 102 rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9,10,63,64 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Dalen. The teachings of Van Dalen as set forth in the above 102 rejection are incorporated herein. The claims rejected herein differ from eg.III in Van Dalen in the following manner. Claims 9,10,63,64 and 67 require that R1 be an alkyl group other than methyl. Note that Van Dalen teaches in addition to methyl, higher alkyls of up to 4 carbon atoms. See the definition of "Z" group corresponding to formula 3 on p.2. Thus it would have been obvious to one skilled

in the art at the time the instant invention was made to modify eg.III by replacing the methyl with higher alkyls and in so doing obtain additional compounds having the uses described by Van Dalen in view of the equivalency teaching outlined above.

Claims 1,2,7,8,11-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Aoki (EP'266). The EP publication describes a compound within the instant scope for various circulatory disorders. See example 24 on p.44.

Claims 13-17 are also rejected herein for the same reason as discussed in the above 102 rejection.

Claims 3-6,9-10,56-66,68-72 and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aoki. The claims rejected herein require substituents on the "Z" ring other than F exemplified by Aoki in eg.24. However, note that Aoki describes as also suitable substituents on the phenyl ring groups such as alkyl, nitro, amino, alkylamino, and acylamino as listed on pages 3-5 for R1/R2. Also halo is taught as a choice for phenyl ring attached to sulfonamide group. See definition for R4/R5 in Aoki on p.3-5. This is embraced by claims 9-10 and 63-64.

Claims 68-72 are also rejected herein for the same reason as discussed in the above Uchida rejection. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to modify eg.24 by replacing the fluoro

with other groups embraced herein or replace the methoxy on phenylsulfonyl with groups such as halo and in so doing obtain additional compounds with the expectation that they too will possess the uses described by Aoki in view of the equivalency teachings outlined above.

The independent species claims are not believed to be obvious variants of Aoki since closest compounds differ in at least 3 respects from closest compound in Aoki, namely at the outer phenyl rings as well as the chain length connecting piperazine with the NS(O)(O) group and thus Aoki is too diffuse to suggest all the necessary modifications to arrive at these compounds. Said species claims would be allowed over the art of record if the 112 rejections are overcome.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Emily Bernhardt
Primary Examiner
Art Unit 1624